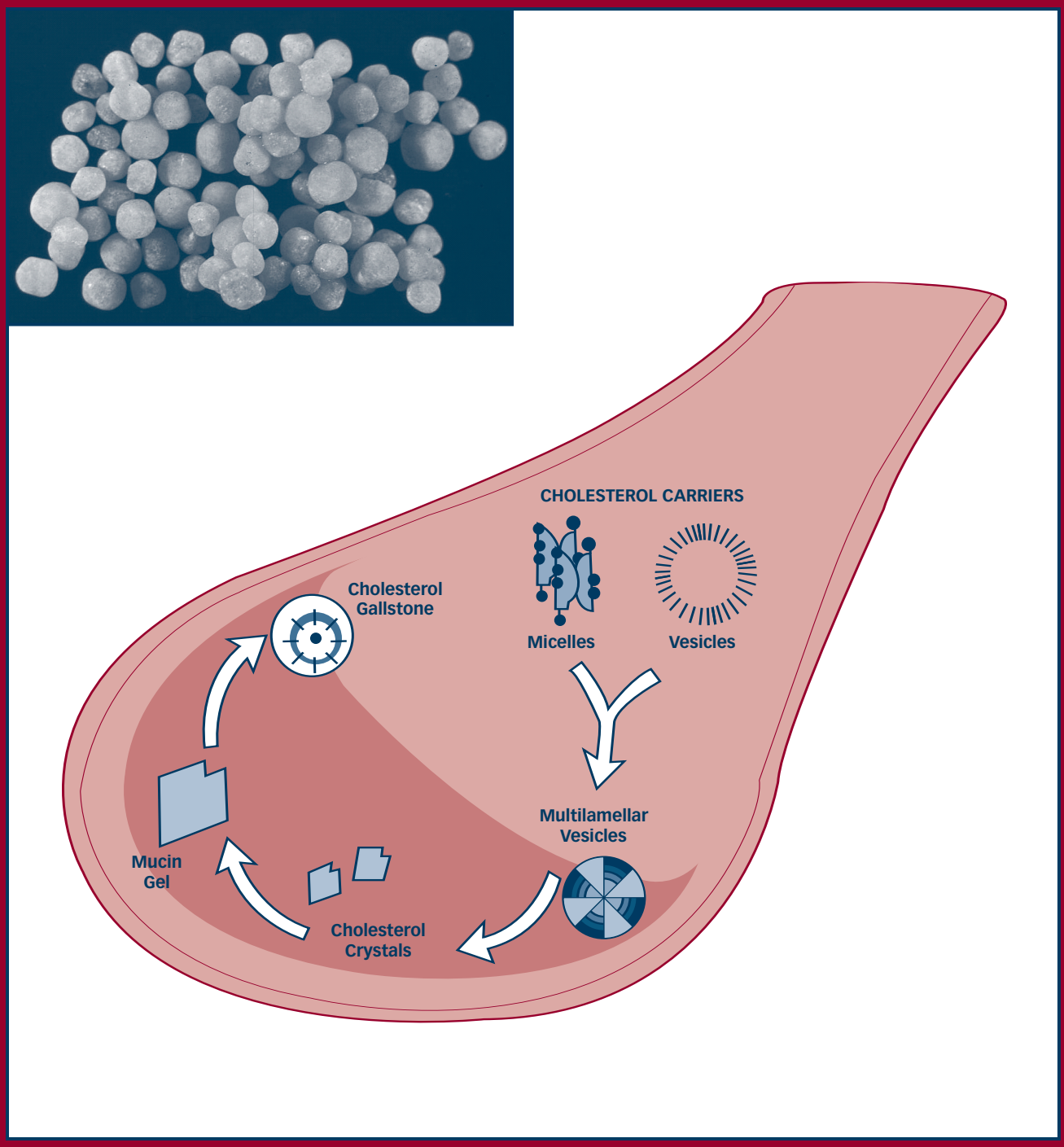

Gallstones in the gallbladder are a common cause of disease in the United States. Most gallstones form when cholesterol in the bile exceeds a certain level and precipitates out as stones. Pictured in the inset photo are several small cholesterol gallstones that have been surgically removed from a patient. The diagram shows the steps involved in cholesterol gallstone formation inside the gallbladder. Photo and diagram: Dr. Sum Lee, University of Washington.

CHAPTER 15: GALLBLADDER AND BILIARY DISEASE

INTRODUCTION AND BACKGROUND

Diseases of the gallbladder and biliary tree include gallstones, acute cholecystitis, acalculous cholecystitis, primary sclerosing cholangitis, biliary atresia, choledochal cysts, gallbladder cancer, and cholangiocarcinoma. These serious diseases can cause considerable morbidity and mortality. Gallstones are by far the most common cause of gallbladder disease.

Gallstones affect at least 20 million Americans (12 percent of adults) and the prevalence of stones appears to be rising. Many gallstones are "silent," but approximately a third eventually lead to symptoms, complications, and need for surgery. Gallstone disease necessitates an estimated 700,000 cholecystectomies per year and led to medical expenses in excess of $6 billion in the year 2000, making it one of the most costly of digestive disorders. At present, 3,000 deaths (0.12 percent of all deaths) are attributed to complications of cholelithiasis and gallbladder disease yearly.

The majority of gallstones are composed of cholesterol, but may also contain calcium and bilirubin. Gallstones form when the concentration of cholesterol or calcium bilirubinates in bile exceeds the limited solubility level and these compounds precipitate out of solution. Gallstones increase in prevalence with age. Risk factors for developing cholesterol gallstones include obesity, major weight loss, medications, genetic predisposition, ethnic background, and, among women, multiparity. Sudden development of symptomatic gallstones can complicate major weight loss, particularly after obesity surgery (gastric bypass). While gallstones rarely result in death, they can complicate management of other diseases, and gallstone pancreatitis can result in prolonged disability and death. Gallstones and other biliary diseases are important risk factors for the development of gallbladder cancer and cholangiocarcinoma, both of which are rare in the general population, but are increasing in frequency. Gallbladder cancer is common in selected populations, such as American Indians and Hispanic Americans of Mexican descent.

A smaller proportion of gallstones are pigment stones. Risk factors for "black" pigment stones include hemolysis and increased enterohepatic cycling of bilirubin, as may occur with ileal disease or intestinal resection. Brown pigment stones are associated with biliary stasis, particularly if there is chronic anaerobic bacterial infection.

Other non-gallbladder-related biliary diseases include primary sclerosing cholangitis, biliary atresia, cystic fibrosis, polycystic liver disease, and malignancies such as cholangiocarcinoma. Many of these conditions are discussed in other parts of this Action Plan. Primary sclerosing cholangitis is the most common of these biliary conditions and is believed to be an autoimmune disease. The diagnosis of primary sclerosing cholangitis is difficult and there are no therapies that are of proven benefit. Primary sclerosing cholangitis is a frequent reason for liver transplantation and is often associated with development of cholangiocarcinoma, a highly malignant neoplasm.

RECENT RESEARCH ADVANCES

Important advances have occurred in the recent past toward defining the causes and optimal treatment of gallbladder and biliary disease.

Understanding Gallstone Formation: The proximal cause of cholesterol gallstones was not well characterized until the early 1970s when NIH-funded investigators demonstrated the importance of the physical chemical nature of bile in maintaining cholesterol in solution. Gallstones were believed to form when the concentration of cholesterol exceeded its solubility in the bile salt and phospholipid-rich bile of humans. Alterations in bile salt, phospholipid, or cholesterol synthesis and secretion appeared to underlie development of gallstones. Animal models were developed for cholesterol gallstone disease, which demonstrated the importance of proteins in bile, as well as the presence of precipitating (nucleation) factors and motility abnormalities of the gallbladder. Recently, inbred strains of mice have been used to demonstrate the importance of genetic factors in the development of gallstones. Studies in the inbred strains of mice have also shown the importance of newly identified bacterial flora colonizing both the distal intestine and gallbladder bile in leading to precipitation of cholesterol and formation of stones. Recent advances in genetics, genomics, and proteomics offer unprecedented opportunities for understanding the molecular basis of the crucial defects leading to gallstone disease. These advances may well lead to practical and effective means of prevention and treatment of gallstone and biliary disease.

Management of Gallbladder and Biliary Disease: The bedrock of management of gallstone disease for more than 100 years has been cholecystectomy. The introduction of laparoscopic techniques in the late 1980s transformed the field and improved medical care of patients with gallstones considerably. At present, over 90 percent of gallbladder surgery is done laparoscopically, which minimizes hospital stay and time out from work and normal activities. At the same time as the advances in laparoscopic surgery were occurring, increasingly sophisticated imaging and endoscopic techniques helped improve the ability to localize and identify biliary tract diseases (including neoplasms and strictures in addition to stones). Endoscopic techniques, such as endoscopic retrograde cholangiopancreatography (ERCP), now allow minimally invasive approaches to diagnosis and management of complicated biliary disease and cancers. Nevertheless, imaging of the gallbladder and biliary tree is problematic, and both diagnosis and monitoring of biliary disease are hampered by the relative inaccessibility of the biliary system and lack of specific means for its visualization.

RESEARCH GOALS

The major goals for research on gallbladder and biliary disease are to develop better means to prevent and treat gallstones and other diseases of the biliary tract.

Gallstones: Pathogenesis and Diagnosis: While fundamental elements of gallstone composition and formation are known, questions of diagnostic and therapeutic importance to gallstone formation and pathogenesis remain. For example, the molecular basis of cholesterol gallstone formation is beginning to be defined with the identification of several *"Lith"* genes associated with cholesterol gallstone susceptibility in murine models on a lithogenic diet.

- *Research Goal:* To further characterize the role of the murine *Lith* genes and their products in causing cholesterol gallstones (Matrix Cell A1).

- *Research Goal:* To apply knowledge of murine *Lith* genes to the identification of homologous genes in humans associated with susceptibility to form cholesterol gallstones (Matrix Cell C2).

While many of the identified *Lith* genes relate to cholesterol and lipid metabolism, important genetic factors related to mucin formation, nucleation factors, and gallbladder motility should also be sought. Epidemiologic and family studies of carriers of these genes would be a necessary complement in this effort to identify genetic contributors to cholesterol gallstone formation in patients.

In addition to exploring the importance of genetic factors in gallstone pathogenesis, microbial factors also warrant further research. Evidence of gallbladder infection with bacteria, including *Helicobacter* species, has been noted in studies of human cholesterol gallstones, but the role that these bacteria might play in gallstone formation remains unknown.

- *Research Goal:* To characterize the role of the enterohepatic bacteria, specifically of the genus *Helicobacter*, in cholesterol gallstone formation in both animal models and human patients (Matrix Cell B2).

Conducting studies in humans in addition to murine models is important in this area because of possible species differences in enterohepatic flora. Future research should also consider the contributions to gallstone formation of microbial interactions with the gallbladder epithelium. If bacterial infection appears to be important in causing gallstones in humans, clinical approaches to treatment and prevention of gallstones using antibiotics to treat and eradicate the bacterial infection should be considered.

In the case of pigment stones, studies should be encouraged to further understanding of the solubility of calcium bilirubinates, including their enzymatic and non-enzymatic hydrolysis, nucleation, precipitation, and polymerization in bile. Better understanding of how to inhibit bacterial beta-glucuronidase and regulate enterohepatic recycling of bilirubin may lead to means of preventing pigment stones.

Of equal interest to delineating the pathogenesis of gallstones is an improved understanding of the origins of pain and inflammation in the gallbladder, both in the presence and the absence of detectable gallstones or biliary tract abnormalities (such as in acalculous cholecystitis, sphincter of Oddi dysfunction, biliary dyskinesia, and post-cholecystectomy biliary pain syndrome). The mechanistic basis for biliary pain, and its seasonal or circadian periodicity, is still not well understood. The cause and appropriate diagnostic evaluation and therapy of the non-gallstone-related biliary dysfunction are particularly challenging. An important way to advance knowledge in this area is through the development of more effective and safer means of management of retained biliary stones. At present, ERCP is commonly used for bile duct stone extraction, but continues to carry some risk of complications.

- *Research Goal:* To develop a cross-sectional and longitudinal cohort study of subjects with biliary pain to allow for analysis of potential risk factors such as genetics, microlithiasis, nucleation factors, gallbladder motility, and sphincter of Oddi function, and pilot studies of treatment and prevention (Matrix Cell B1).

Translation of knowledge gleaned from basic and clinical research into clinically usable diagnostic tools could improve the care of gallbladder and biliary disease. For example, biomarkers of lithogenic bile identified through proteomic or metabolomic assays of plasma or urine could permit the early identification of individuals at high risk of developing gallstones.

- *Research Goal:* To identify biomarkers in plasma or urine that indicate lithogenicity of bile (Matrix Cell B3).

With these diagnostic tools available, it might be possible to design strategies to prevent cholesterol gallstone disease.

- *Research Goal:* To develop and test a practical and effective approach to prevention of gallstones in high-risk populations (Matrix Cell C3).

Primary Sclerosing Cholangitis: Pathogenesis and Management: Recent estimates of the prevalence of cholangiopathies—diseases that affect the biliary epithelium such as primary sclerosing cholangitis (PSC)—have shown that these conditions are more common in the U.S. population than previously estimated. Whereas the etiology of PSC is unknown, its co-incidence with inflammatory bowel disease suggests that autoimmunity is responsible for inflammatory and fibrotic damage to the bile ducts in this condition. However, the role of autoimmunity in the etiology of PSC is still unsettled and other possible mechanisms, such as infection, environmental exposures, and heightened immune responses to enteric bacteria deserve careful analysis. An animal model of PSC would greatly facilitate this research.

- *Research Goal:* To develop a reliable small animal model for the cholangiopathies to allow for research on pathogenesis, prevention, and treatment (Matrix Cell A2; see also Chapter 9, B3).

Gallbladder Cancer and Cholangiocarcinoma Detection: Cholangiocarcinoma refers to adenocarcinomas affecting the biliary tree that can be either intra- or extra-hepatic and are often related to chronic biliary diseases such as PSC. Gallbladder cancer refers to adenocarcinoma arising in the gallbladder and typically occurs in patients with gallstones and chronic cholecystitis. Cholangiocarcinoma and gallbladder cancers are usually detected at a late stage, and adequate therapies are lacking.

In certain high-risk populations, the incidence of gallbladder cancer has been rising. An important research goal is to improve early diagnosis and management of these cancers, so that necessary steps, such as liver transplantation for PSC or cholecystectomy for gallstones, can be taken to prevent these fatal cancers. The identification of genetic or biological markers for gallbladder cancer and cholangiocarcinoma in high-risk populations would facilitate diagnosis and early detection.

- *Research Goal:* To develop a noninvasive biomarker for cholangiocarcinoma (Matrix Cell C2; see also Chapter 9, C2).

This research goal would benefit from the creation of a database to collect information on a cohort of patients at high risk of gallbladder cancer, such as American Indians, for large-scale studies of novel diagnostic and therapeutic approaches.

- *Research Goal:* To establish a cohort of patients at high risk of gallbladder cancer for studies of risk factors, genetic predisposition, early detection, prevention, and management (Matrix Cell C1).

Biliary Tract and Gallbladder Imaging: Effective diagnosis and monitoring of disease in the biliary tract is hindered by the structure's relative inaccessibility to biopsy and the limits of available imaging technology. Current methods to visualize the biliary tract are often invasive or not sufficiently informative for diagnosis and staging of disease.

- *Research Goal:* To develop innovative and effective molecular imaging techniques to visualize the biliary tract that provide information on anatomy,

physiology, and pathology (e.g., inflammation, neoplasia) (Matrix Cell A3; see also Chapter 16, A3).

Molecular imaging might provide improved diagnostic assessment, early detection and staging of neoplasia, and noninvasive evaluation of gallbladder motility, degree of inflammation, sphincter of Oddi function, and physical composition of gallstones or sludge within the biliary tract. In addition, these improved imaging techniques might provide a means to monitor the effectiveness of a therapeutic regimen by directly assessing changes in disease activity.

STEPS TO ACHIEVE RESEARCH GOALS

Progress in gallbladder disease research would be strengthened with the availability of more advanced molecular tools, including molecular libraries of genes expressed by the liver and gallbladder, proteomic and metabolomic resources, and molecular probes and antibodies, such as those needed to measure murine *Lith* and human *LITH* genes and their products.

The development of molecular markers for lithogenic bile and innovative molecular imaging technology to visualize the biliary tract and gallbladder requires the formation of interdisciplinary teams of investigators, including clinicians, endoscopists, radiologists, biomedical engineers, physical chemists, molecular biologists, and geneticists.

Large-scale clinical studies of populations at high risk of developing gallbladder disease require collaborative networks of clinical centers, either existing or newly established. Existing networks and clinical trials include: (1) the Longitudinal Assessment of Bariatric Surgery (LABS) Consortium, which could provide patient materials to evaluate biomarkers for lithogenic bile and the effects of obesity and rapid weight loss on formation of gallstones, and (2) the High-Dose Ursodiol Trial in PSC, which could be used to help identify biomarkers for disease progression or cholangiocarcinoma.

The ability to pursue the promising research opportunities now available in the area of gallbladder and biliary disease requires a pool of new, highly trained investigators to conduct and continue this research. Encouraging the training and career development of more young investigators is important to the future success of these research efforts.

Matrix of Research Goals in Gallbladder and Biliary Disease

	Short Term (0-3 years)	Intermediate Term (4-6 years)	Long Term (7-10 years)
High Risk	**A3.** Develop molecular imaging techniques for visualization of biliary tract that would provide accurate assessment of size, shape, position, motility, and inflammation, as well as a means of early detection and staging of neoplasia.	**B3.** Identify plasma or urine markers for lithogenicity of bile using proteomics or metabolomics.	**C3.** Develop practical and effective approach to or means of prevention of cholesterol gallstones in high-risk populations.
Intermediate Risk	**A2.** Develop small animal model for cholangiopathies that would allow analysis of effects of chronic necroinflammation on biliary epithelium.	**B2.** Characterize role of enterohepatic species of *Helicobacter* and other candidate bacteria in development of cholesterol gallstones in both mice and humans.	**C2.** Identify at least 5 human *LITH* genes associated with increased risk of gallstones, based upon homology with murine genes and family studies. Develop noninvasive biomarker for cholangio-carcinoma.
Low Risk	**A1.** Fully characterize at least 10 murine Lith genes related to cholesterol gallstones.	**B1.** Develop cohort study of calculous and acalculous biliary pain to allow for analysis of risk factors and roles of genetic factors, microlithiasis, gallbladder motility, sphincter of Oddi dysfunction, and nucleation factors.	**C1.** Establish prospective database on cohort of patients with high risk of gallbladder cancer (e.g., American Indians) to allow development and assessment of means of early diagnosis and management.